Formulation and Evaluation of the Floating Controlled Release Tablet of Fosinopril sodium by using a hydrophilic polymer matrix

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Abstract

Objectives: The purpose of the study was to develop a floating Controlled tablet of Fosinopril sodium by using a hydrophilic polymer matrix to improve the therapeutic effectiveness of the drug.
Methods: Fosinopril sodium tablets were prepared by direct compression and evaluated for FTIR of Pure Drug, drug-excipients compatibility, Pre and Post Evaluation Studies, in-vitro Studies study, Stability Study..
Results: DSC and FT-IR studies confirmed the absence of incompatibility and were found stable at refrigerator temperature (2-8°C) and at 25ºC/60% RH. The Pre evaluation like carr's idex, bulk density, tapped density etc was performed. For post evaluation the Cumulative % of drug release at 10 hrs was 90.91, 87.02, 83.32 and 75.62 for the formulation F1, F2, F3 and F4 respectively. More than 85% of drug released in 7 hrs, 9 hrs, 11 hrs and 13hrs for the formulation F1, F2, F3 and F4 respectively. So, it was indicated that the drug release rate is significantly reduced with time at higher concentration of SFG. From the results it was found that cumulative percentage of drug release was decreased with the concentration of SFG is increased. That was lower in formulation F1 than F4. From the results, it was much cleared that the formulation F8 and F9 was provided well controlled drug release pattern from the swelling and erodible diffusion matrix and these formulations were nearer to theoretically developed dissolution profile among all the formulation developed.

Key Words: Floating, erodible diffusion, prodrug, Sterculia Foetida Gum

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Introduction

Formulation of FDDS containing suitable drug candidates which would remain in the stomach and/or upper part of GIT for a prolonged period of time there by maximizing the drug release at desired site within the time before GRDFs left the stomach and/or upper part of the GIT.

These systems are also called as hydrodynamically balance systems (HBS). It is an oral dosage form designed to prolong the residence time of the dosage form within the gastrointestinal track. To provide good floating behavior in the stomach, the density of the floating drug delivery system (FDDS) should be less than that of gastric content (<1.0049 g/cm 3).[1-2]

The drug Fosinopril sodium which has been selected to be formulated as FDDS, has the following characteristics, It is stable in gastric acidic medium, It has a narrow absorption window in GIT (Stomach), Has a pH dependent absorption and maximum absorption in acidic region having pH less than 2.5, Highly soluble at acidic pH, Has no effect of food on absorption. It is quite unstable in colonic environment.[3-4]

Fosinopril is a phosphinic acid-containing ester prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is rapidly hydrolyzed to fosinoprilat, its principle active metabolite. Fosinoprilat inhibits ACE

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the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Fosinopril may be used to treat mild to moderate hypertension, as an adjunct in the treatment of congestive heart failure, and to slow the rate of progression of renal disease in hypertensive individuals with diabetes mellitus and microalbuminuria or overt nephropathy.[5-8]

Material & Method

Material

Fosinopril sodium, Sterculia Foetida Gum (SFG), HPMC K 15 M, Acrypol 934, PVP K 30, NaHCO 3, Lactose, Talc, Mg. Stearate and IPA.

Method

Identification of Drug

FTIR

The pure drug i.e. Fosinopril sodium and the mixture of drug with various polymers used in the preparation of floating tablet formulations were analysed by FT-IR spectroscopy to know the compatibility with each other. The FTIR spectra were taken on a Shimadzu (FTIR-8300) instrument for all samples and it was measured by KBr disk method.

Differential scanning Calorimetry (DSC)

The pure drug i.e. Fosinopril sodium and the mixture of drug with various polymers used in the preparation of floating tablet formulations were also measured by DSC to study about the physicochemical compatibility with each other. Thermograms of the drug alone and drug - polymer physical mixture were obtained from a Shimadzu (DSC- 60) instrument. The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated over a temperature range of (50-300 °C) at a constant scanning.

Standard calibration curve of Fosinopril Sodium in 0.1N HCL

The Calibration curve of Fosinopril sodium in 0.1N HCL (pH1.2) was found to be linear at the concentration of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml. All diluted solutions were analyzed at 250 nm wavelength using Shimadzu 1800 UV/ Visible double beam Spectrophotometer and 0.1 N HCL solution was taken as reference standard for base line correction. Absorption for each concentration was measured in triplicate and average of it was used for the preparation of standard curve.

Preparation of Fosinopril sodium Floating Tablet

Fosinopril sodium controlled release floating tablets were prepared by wet granulation techniques using different concentrations of various polymers. To prepare tablet, weighed all ingredients except talc and magnesium stearate and shifted through sieve no 40 then blend uniformly in glass mortar with pestle. After sufficient mixing, the blend was wetted by adding sufficient quantity of isopropyl alcohol as a granulating agent. Prepared wet mass was granulated by passing through sieve no 18. Prepared granules were dried at 50 ^{0}C – 60 ^{0}C for 20 min in hot air oven. After drying, dried granules were lubricated by adding sufficient quantity of magnesium stearate and talc for 5 min. Then, the granules were ready for compression. The tablets were compressed using 6 mm punch on 8 station rotary punching machine. The weight of tablets was kept constant for tablets of all formulations, which was 85 mg and it is shown in Table 1.

Table 1: Fosinopril sodium-controlled release floating tablet composition.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	10	10	10	10	10	10	10	10	10	10	10	10
SFG	4	8	12	16	--	--	--	12	10	8	--	--
HPMC K15M	--	--	--	--	8	12	16	--	--	--	8	10
Acrypol 934	--	--	--	--	--	--	--	4	6	8	8	6
$NaHCO_3$	10	10	10	10	10	10	10	10	10	10	10	10
PVP K 30	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	51	47	43	39	47	43	39	39	39	39	39	39
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3

IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**	**85**

Pre-Compression Evaluation [9-13]

Bulk density (BD)

Bulk density (BD) = M / V_b Where,
M = Mass of powder taken (g), V_b= Bulk Volume (cm^3)

Tapped Density (TD) [60]

Tapped density (TD) = M/V_t Where,
M = Mass of powder taken (g)
V_t = Tapped volume (cm^3)

Compressibility Index (CI) [60]

Compressibility index is calculated from BD and TD using the formula,
CI = {(TD - BD) / TD} x 100 Where,
TD = Tapped Density (g/cm^3)
D = Bulk Density (g/cm^3)

Hausner Ratio (HR) [60]

Hausner Ratio is calculated from BD and TD using the formula,
Hausner ratio = TD / BD Where,
TD = Tapped Density (g/cm^3)
BD = Bulk Density (g/cm^3)

Angle of Repose (AR) [61]

Angle of repose (θ) $= \tan^{-1}(h / r)$ Where, h = Hight of pile, r = Radius of pile
. The AR for the granules of formulation F1 to F4.

Post Evaluation of Fosinopril sodium Controlled Release Floating Tablets [14-17]

Weight variation (WV)

Twenty tablets were randomly selected from each formulation and individually weighed in milligrams. The average weight and standard deviation of 20 tablets was calculated. The weight variation test is passing if not more than two of the individual tablet weight deviate from the average weight from specified percentages deviation limit and none deviate from average weight by more than twice the percentage deviation.

Thickness (T)

Twenty tablets were randomly selected from each formulation and measured thickness in millimeter of each tablet by Vernier Calliper.

Diameter (D)

Twenty tablets were randomly selected from each formulation and measured diameter in millimeter of each tablet by Vernier Calliper

Hardness (H)

Twenty tablets were randomly selected from each formulation and measured hardness in kg/cm^2 using Monsanto type hardness tester.

Friability (F)

Twenty tablets were randomly selected from each formulation and after weighing accurately placed in the electrolab friabilator. The rotation speed of friabilator was kept at 20 rpm for 5 minute. After 5 minutes, the tablets were dedusted and weighed again. The percentage friability is measured using the formula,
Percentage of Friability (% F) = $[1 - (W/W_0)] \times 100$
Where,
W_0 = Initial weight of tablets (g)
W = Final weight of tablets after rotation (g)

Assay

10 tablets were randomly selected from each formulation and crushed to a fine powder in mortar with pestle. Weigh accurately equivalent to 8 mg of Perindopril Erbumine from fine powder then transfer in 100 ml volumetric flask, 100 ml of 0.1 N HCL was added to dissolve and sonicated for 20 minutes. After Sonication, insoluble matter was allowed to settle. The resultant solution was diluted to get concentration about 8.5 µg/ml Perindopril Erbumine in 0.1 N HCL. Resulting solution was filtered through whatman filter paper. Absorbance of final resultant solution was measured in U V Spectrophotometer at 207 nm. The concentration of drug present in final diluted solution was calculated from the calibration plot of Perindopril Erbumine in 0.1 N HCL and find out actual drug content present in it.

In vitro dissolution study

The *In-vitro* dissolution study for the tablet of each formulation was conducted as per United States Pharmacopoeia type II apparatus. The rotating

paddle method was used to study the drug release from the tablets. Dissolution medium 900 ml of 0.1 N HCl (pH 1.2) was placed in dissolution vessel. The release was performed at 37 ^{0}C ± 0.5 ^{0}C and at a rotational speed of paddle about 50 rpm. Tablets were placed in each dissolution vessel. The 5 ml samples were withdrawn at the time interval of one hour for 16 hrs. The collected samples were filtered through Whatman filter paper No. 40 and analyzed for drug content by UV Spectrophotometer. The absorbance for each sample was measured at 207 nm and the concentration of drug present was calculated using calibration plot of Perindopril Erbumine. Then, the cumulative percentage amount of drug released at each time interval was calculated using the formula.

Cumulative amount of drug release = C × DF × DM

Where,

C = Concentration of drug at each time interval (µg/ml)

DF = Dilution Factor is 1.

DM = Dissolution Medium (900 ml)

Stability Study [18]

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product, which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Formulations were selected for stability from the optimization study. The tablets of optimized formulation were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines.

All the selected tablet samples were stored at 25 ^{0}C / 60% RH and at 40 ^{0}C / 75% RH in air tight high density ethylene bottles for 2 months in humidity chamber. The tablet samples were taken out at 0, 30 and 60 days. All the sample tablets were evaluated for the different physicochemical parameters i.e. floating properties, swelling study and percentage of drug release. The results are represented in the Table 6.20.

Result & Discussion

A plot of Absorption at 207 nm Vs Concentration (µg/ml) is plotted and find out regression equation from it to determine unknown concentration of drug. The plot is shown in **Figure 1.**

In the present investigation for the development of Fosinopril sodium controlled release floating tablet, Fosinopril sodium was selected as a model drug and its antihypertensive activity has been reported. Polymers viz; Sterculia Foetida Gum (SFG), HPMC K15M and Acrypol 934 were selected to develop the controlled release formulation.The Pure Drug spectra with excipient of FTIR are shown in **Figure 2-6**. Fosinopril sodium contains one C=O, one COO^{--}, one COOH, one 2^0 amine and one 3^0 amine which have characteristic peak values range around 1725 - 1705 cm^{-1}, 1300 - 1000 cm^{-1}, 1320 - 1210 cm^{-1}, 1640 – 1560 cm^{-1} and 1360 – 1080 cm^{-1}respectively. IR spectra was shown that characteristic peak was observed at 1750 cm^{-1}(C=O), 1200 cm^{-1}(COO^{--}), 1300 cm^{-1}(COOH), 1650 cm^{-1} (2^0amine) and 1350 cm^{-1}(3^0amine) in all spectra while new band or shift in characteristic band were not seen in the mixtures. The physical incompatibility study was done by DSC. It is useful in the investigation of solid-state interactions; hence, thermograms were generated for both pure drug and drug excipients mixtures.Fig 7

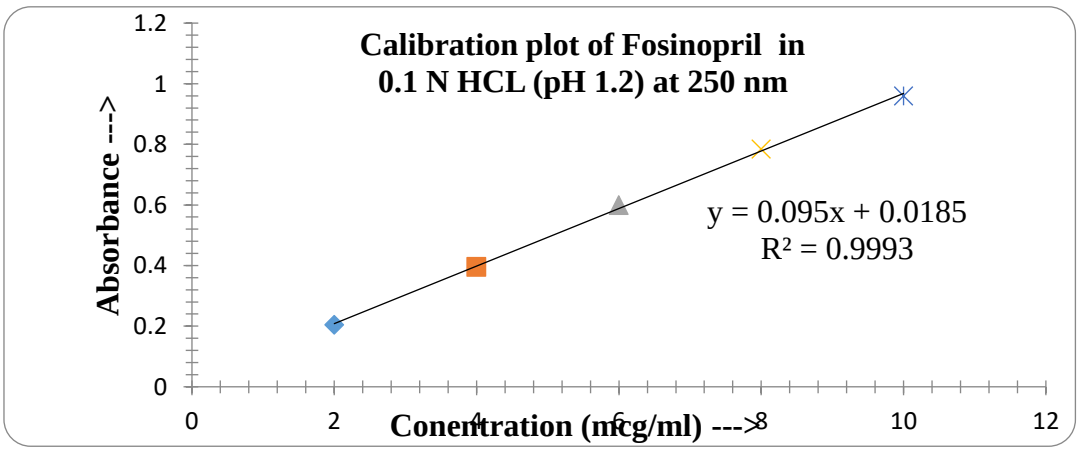

Figure 1: Calibration curve of Fosinopril sodium in 0.1N HCL

Figure 2: IR spectra of Fosinopril sodium

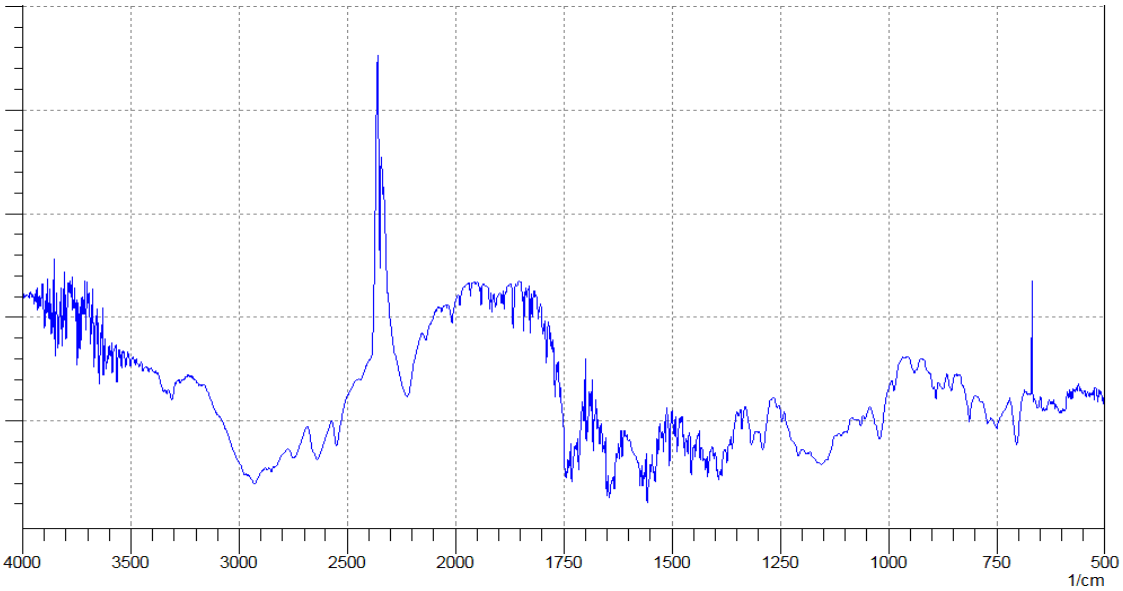

Figure 3: IR spectra of Fosinopril sodium and SFG

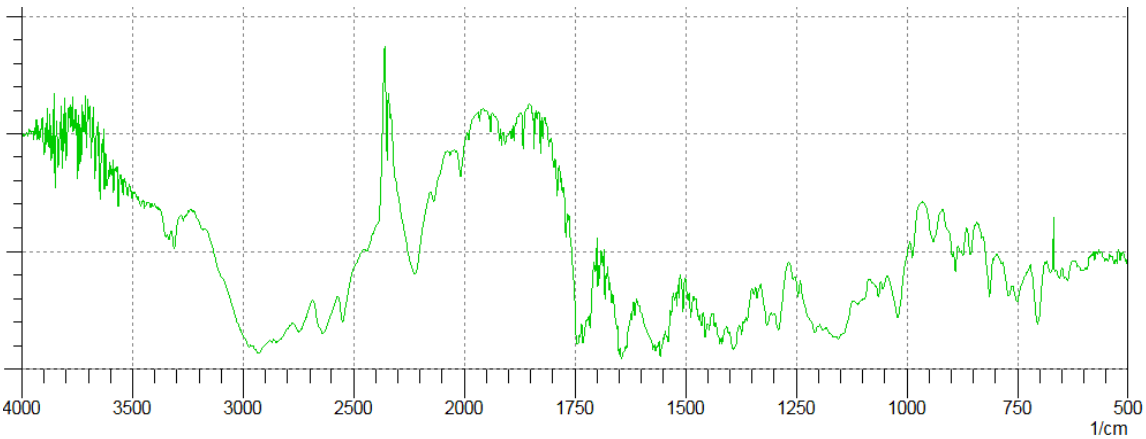

Figure 4: IR spectra of Fosinopril sodium and HPMC K 15

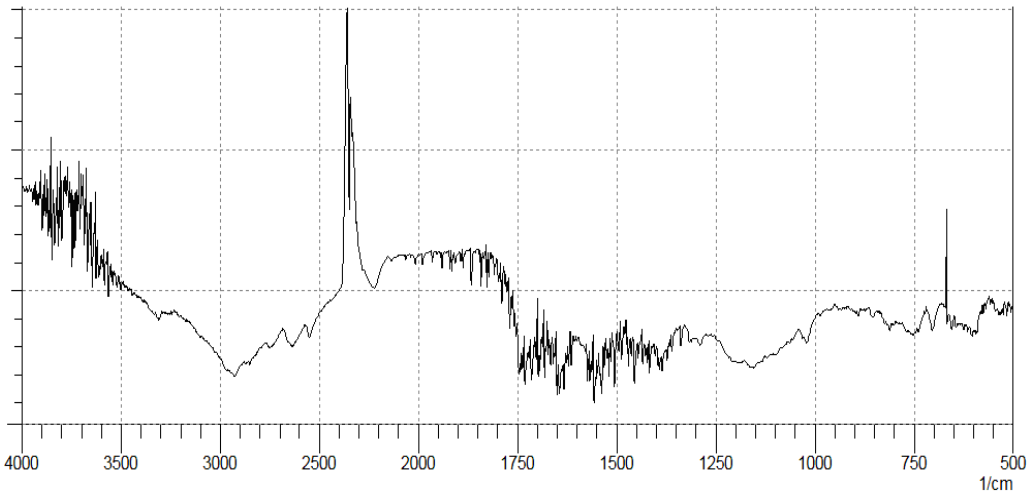

Figure 5: IR spectra of Fosinopril sodium and Acrypol 934

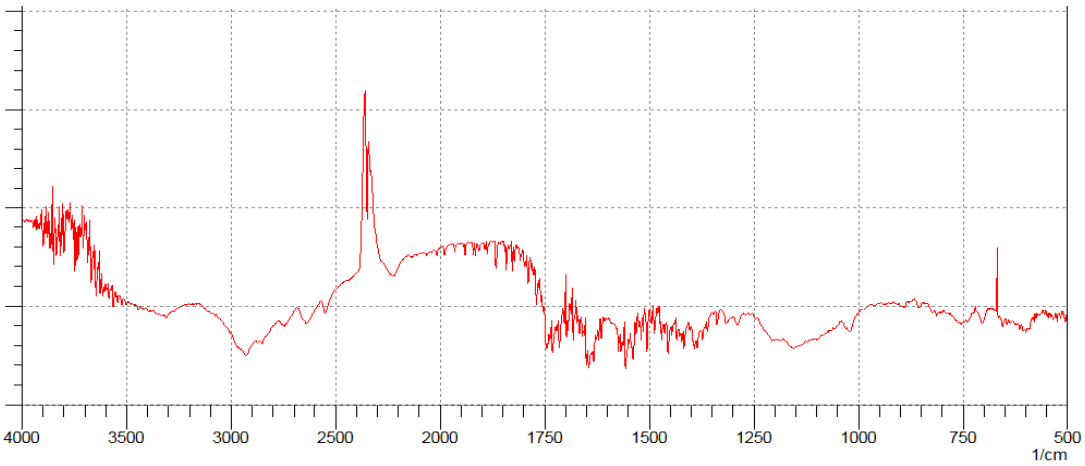

Figure 6: IR spectra of Fosinopril sodium, Acrypol 934, HPMC K 15 and SFG

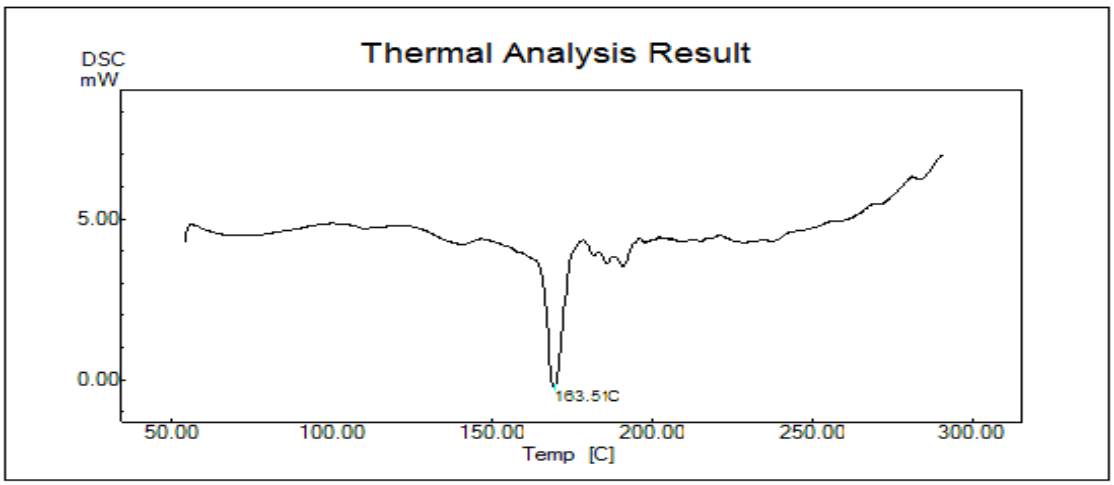

Figure 7: DSC of Fosinopril sodium

The value of angle of repose (AR) suggest that formulation F1 and F2 observed poor flowability while Formulation F3 and F4 shown good and excellent flowability. The flowability of prepared granules was improved by increasing the concentration of SFG. It might be due to the good bonding ability during wetting, provide sufficient size and density by minimizing fines in granulation. The value of angle of repose (AR) suggest that formulation F1 and F2 observed poor flowability

while Formulation F3 and F4 shown good and excellent flowability.

The flowability of prepared granules was improved by increasing the concentration of SFG. It might be due to the good bonding ability during wetting, provide sufficient size and density by minimizing fines in granulation. The compressibility index (CI) for the formulation F4 showed excellent flowability. Here, also proved that by increasing the concentration of SFG, the flowability of prepared granules improves with respect to the compressibility index. It might be due to its geometrical shape that is triangular. The tablets of formulation F1 to F4 were evaluated for its physical characteristics. Average weight (AW), Hardness (H), Thickness (T). There was no significant difference observed in AW, H, T and D. So, it was proved that there was uniformity in physical parameter of tablet prepared for F1 to F4. There was no effect of concentration of SFG on physical parameter [viz; AW, H, T and D] of tablet but in friability of tablets it was observed. Formulation F4 was showed lower value of friability than the formulation F1. From the results it was found that cumulative percentage of drug release was decreased with the concentration of SFG is increased. That was lower in formulation F1 than F4. Formulation F8 to F12 was developed by using the combination of polymers SFG and HPMC K 15 M with polymer Acrypol 934. Acrypol 934 is the polymer of acrylic acid cross linked polyalkenyl ethers or divinyl glycol and network structure of polymer chains interconnected by cross-links. The physical parameters of tablets were found to be good but it was observed that the hardness and friability improved with the concentration of Acrypol 934. Because the value of hardness in F10 (5.95 kg/cm^2) and in F11 (5.90 kg/cm^2), it was higher than the tablet of F8 (5.75 kg/cm^2) and of F11 (5.75 kg/cm^2) respectively. Similarly friability also improved due to the hardness improved.

Cumulative % of drug release at 10 hrs was 90.91, 87.02, 83.32 and 75.62 for the formulation F1, F2, F3 and F4 respectively. More than 85% of drug released in 7 hrs, 9 hrs, 11 hrs and 13hrs for the formulation F1, F2, F3 and F4 respectively. So, it was indicated that the drug release rate is significantly reduced with time at higher concentration of SFG. From the results it was found that cumulative percentage of drug release was decreased with the concentration of SFG is increased. That was lower in formulation F1 than F4. But, at the higher concentration drug release rate was near to zero order release than lower concentration of SFG till the 11 to 12 hrs. It might be happened due to the slowly diffusion of drug from the highly viscous gelatinous layer formed over the surface of dosage form at higher concentration. But in comparison with the formulation containing SFG, the drug release rate was well controlled in formulation F4 than F7 till the 12 hr. These results might be observed due to the higher gelling capacity of SFG than HPMC K15M upon hydration and controllable high swelling property as well. So, from the result it was found that well controlled drug release profile obtained by using SFG than HPMC K15M at same level of concentration. From the results, it was cleared that F8 and F9 was shown well controlled dissolution profile. There might be too slow release rate of drug from the developed formulation F10. It might be due to the higher concentration of acrypol 934. And as mentioned earlier, at the higher concentration acrypol gives higher viscosity as well as gelling properties. Higher level of gelling and viscosity might be reduced drug release property significantly. Fig 3 to 5

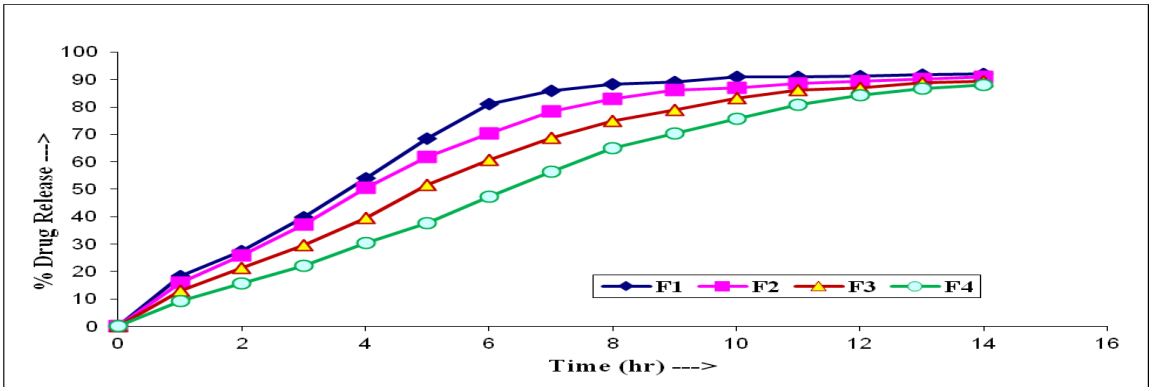

Figure 8: Plot of cumulative percentage of drug release vs time for F1 to F4

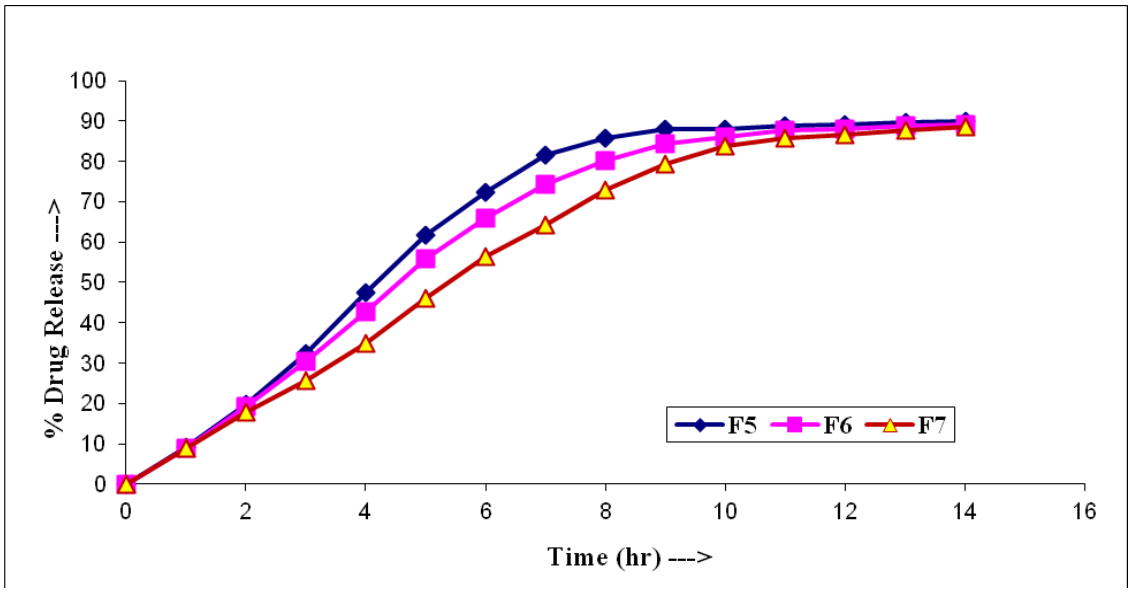

Figure 9: Plot of Cumulative percentage of drug release with time for F5 to F7

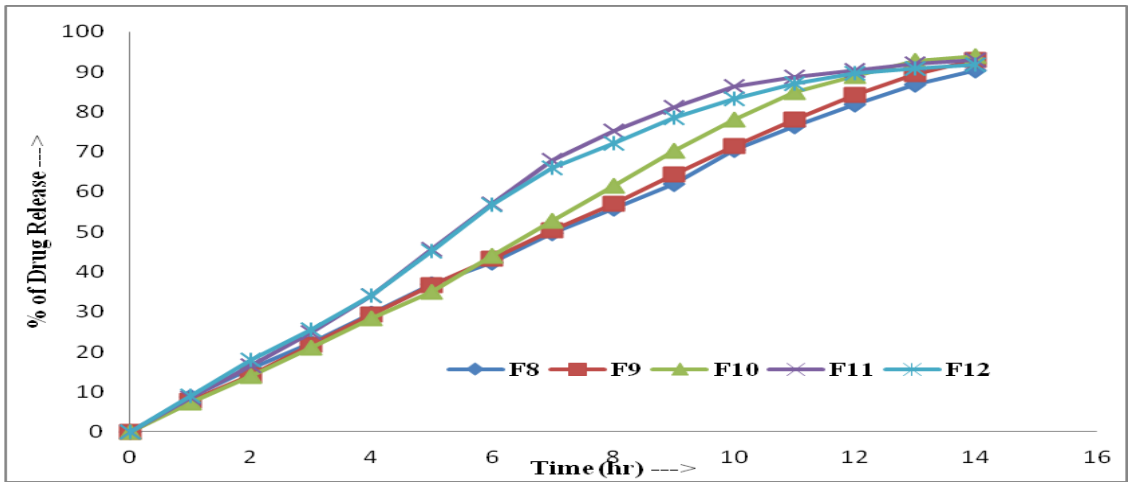

Figure 10: Plot of Cumulative percentage of drug release with time for F8 to F10

For the stability study, the tablets of optimized formulation (A4) were stored at 25 ^{0}C / 60 RH and at 40 ^{0}C / 75% RH in humidity chamber for 60 days. The samples were withdrawn at 30 days and 60 day. All the sample tablets were evaluated for floating properties, swelling studies and dissolution studies. From the results, it was found that there was no considerable difference observed in all parameters and the results were represented shown in **Table 2**.

Table 2: Stability study of optimized formulation at 25 ^{0}C / 60 RH and at 40 ^{0}C / 75% RH

SN	Parameter	Initial	Stability Results					
			25 ^{0}C / 60 RH			40 ^{0}C / 75% RH		
			15 days	30 days	60 days	15 days	30 days	60 days
1	FLT (seconds)	83	81	83	80	82	81	81
2	TFT (seconds)	≥18	≥18	≥18	≥18	≥18	≥18	≥18
3	SWI at 12 hrs	≥102.5	≥104.5	≥102.3	≥102.7	≥102.2	≥103.5	≥102.9
4	Assay (%)	99.91	99.46	99.98	99.94	99.91	99.97	99.96
5	% of drug	40.09	38.12	40.82	40.32	40.74	39.09	40.36

	Release (6 hr)							
6	% of drug Release (12 hr)	80.12	81.56	82.79	82.13	80.53	80.04	80.81

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